



<b>Office Action Summary</b>	Application No. <b>09/020,716</b>	Applicant(s) <b>Rudolf Jung, et al.</b>
	Examiner <b>Amy Nelson</b>	Group Art Unit <b>1649</b>

Responsive to communication(s) filed on Feb 9, 1998

- This action is **FINAL**.
- Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

#### Disposition of Claims

- Claim(s) 1-21 is/are pending in the application.
- Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- Claim(s) \_\_\_\_\_ is/are allowed.
- Claim(s) 1-21 is/are rejected.
- Claim(s) \_\_\_\_\_ is/are objected to.
- Claims \_\_\_\_\_ are subject to restriction or election requirement.

#### Application Papers

- See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- The proposed drawing correction, filed on \_\_\_\_\_ is  approved  disapproved.
- The specification is objected to by the Examiner.
- The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

- Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- All  Some\*  None of the CERTIFIED copies of the priority documents have been received.
- received in Application No. (Series Code/Serial Number) \_\_\_\_\_.
- received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
- \*Certified copies not received: \_\_\_\_\_
- Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

- Notice of References Cited, PTO-892
- Information Disclosure Statement(s), PTO-1449, Paper No(s). 5
- Interview Summary, PTO-413
- Notice of Draftsperson's Patent Drawing Review, PTO-948
- Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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## **DETAILED ACTION**

### ***Claim Objections***

1. Claims 1 and 5 are objected to because of the following informalities:

At Claim 1, lines 1-2, "is characterized as having" should be changed to --has--.

At Claim 5, line 2, "oats" should be changed to --oat--.

### ***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn broadly toward a transformed cereal plant seed with an elevated level of at least one amino acid. Applicant has described transformed maize seed with an elevated level of lysine by transformation with a modified hordothionine gene. Applicant does not describe other transformed cereal plant seed modified in other amino acids transformed with other

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modified or unmodified genes, and hence it is not clear from the instant specification that the Applicant was in possession of the invention as broadly claimed.

See *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

4. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to transformed cereal plant seed having an elevated lysine content comprising the modified hordothionin gene of SEQ ID NO:2 (HT12), vectors, plant cells and transformed plants comprising said modified hordothionin gene, and a method for increasing seed lysine content by transformation with said modified hordothionin gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are indefinite for the reasons discussed below. However, it appears that Applicant broadly claims a transformed cereal plant seed with an elevated level of at least one amino acid. Applicant also claims vectors comprising an endosperm-specific promoter operably linked to a gene which encodes a protein with an elevated level of an amino acid, a plant cell transformed therewith, and a method of enhancing the nutritional value of plant seed therewith.

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Applicant teaches isolation of the alpha hordothionin gene (HT; SEQ ID NO:1) from *Hordeum vulgare* by RT-PCR, and Applicant teaches production of a mutated gene (HT12; SEQ ID NO:2) by site-directed mutagenesis to introduce 12 lysine residues into the encoded protein (Example 1). Applicant teaches construction of vectors comprising the HT12 gene operably linked to the zein, globulin 1, or waxy promoter and terminator sequences (SEQ ID NO:3, 4, 5, respectively), and teaches construction of vectors comprising a modified ESA gene or a modified BHL gene operably linked to the zein promoter and terminator sequences (SEQ ID NO:6 and 7, respectively) (Example 2). Applicant also teaches transformation of maize plants by bombardment of immature embryos (Example 3), and Applicant teaches analysis of seed from transgenic maize transformed with each of the HT12 constructs. Applicant teaches by ELISA and SDS-PAGE that the HT12 protein is expressed and processed correctly, and Applicant teaches that the lysine content in cornmeal produced from whole kernels of maize is increased with respect to untransformed maize (Example 4; Table 1).

*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations for determining whether or not undue experimentation would be necessary to practice an invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

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The state of the art for amino acid substitution is highly unpredictable. In particular, the role of specific amino acids in protein function cannot be reliably predicted, and the effect of amino acid substitution on protein activity must be determined empirically. Furthermore, the state of the art for modification of gene expression or of phenotypic characteristics in plants by genetic transformation is highly unpredictable and hence significant guidance is required to practice the art without undue experimentation. The specific effects of given promoters, leaders, DNA sequences, and terminator sequences on gene expression in transformed plants can not be anticipated reliably and must be determined empirically (Plant Mol. Biol. 32: 393-405, 1996, abstract, pp. 402-403). In genetically modified plants, the introduced transgenes are sometimes not expressed, and they can also result in co-suppression effects. None of these effects are predictable, and the mechanisms of gene silencing are still not fully understood (Ann. Bot. 79: 3-12, 1997, abstract, p. 9). Moreover, the phenotypic characteristics that will result from expression of a given DNA construct can not be reliably predicted. In fact, often the expected phenotypic result is not achieved. For example, antisense expression of polygalacturonase gene in transgenic tomato had no effect on fruit softening (Nature 334: 724-726, 1988, p. 725).

Given the unpredictability in the art, the instant invention is not enabled given the lack of guidance in the specification with regard to what amino acid substitutions other than the 12 amino acid substitutions of SEQ ID NO:2 in what gene other than the barley hordothionine gene can be expressed in a transgenic plant, resulting in an elevated level of an amino acid other than lysine. Applicant provides no guidance for other locations for and types of amino acid substitutions in the

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barley hordothionine gene which would not result in a loss of protein activity and which would result in an increase in the level of the substituted amino acid upon transformation of plants. In the absence of such guidance, undue trial and error experimentation would be required to screen through the vast number of potential amino acid substitutions to determine the locations and amino acids which could be successfully substituted. Furthermore, Applicant has not provided guidance with respect to other genes which could be mutated and expressed in plants, which would likewise result in increased levels of lysine in transformed plants. Although Applicant briefly mentions the ESA and the BHL genes, Applicant does not provide specific guidance with respect to locations of and amino acids which could be substituted, resulting in an enhanced level of the substituted amino acid in transgenic plants. Also, although Claims 10-12 are indefinite as discussed below, it does not appear that Applicant has provided guidance for the specific elevated levels of lysine. Whereas Applicant teaches some increase in lysine content maize kernels when the mutant HT12 gene is expressed behind the waxy or zein promoter in transgenic maize plants (Table 1), it is not clear that the increases are greater than 20% by weight, for example, especially because the units of measurement in are not clear from the table. Given the unpredictability in the art, the scope of the claimed invention is not commensurate with the teachings of the specification, and hence the invention is not enabled throughout the broad scope.

When the *Wands* factors are weighed it is concluded that undue experimentation would be required to practice the invention throughout the scope of the claims, and therefore the invention is not enabled.

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5. Claims 1-18, 20, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

At Claim 1, line 3, “a seed from a corresponding plant which has not been transformed” should be changed to --a corresponding untransformed cereal plant seed-- for clarity.

At Claim 1, line 5, the language “or combinations thereof and optionally” is confusing and indefinite. It is not clear what is encompassed by the claim. Appropriate correction is required.

At Claim 2, line 2, the language “or ... and optionally...” is indefinite. It is not clear what is encompassed by the claim. Appropriate correction is required.

Claim 4 is indefinite in its recitation of “the preselected amino acid is lysine and a sulfur-containing amino acid.” It is unclear how the amino acid can be lysine and also be a sulfur-containing amino acid. Appropriate correction is required.

In Claim 8, the phrase “the protein is ... derivatives of each protein” is improper English, due to the lack of agreement between the singular verb and plural direct object. Appropriate correction is required.

At Claim 8, line 3, “derivatives” is indefinite. There are many different types of derivatives, and Applicant has not clearly defined the term. Hence, it is not known what is encompassed by the claim. Appropriate correction is required to clarify the metes and bounds of the claimed invention.

At Claims 10-12, line 2, the phrase “about ... percent by weight to about 10 times greater” is indefinite. The lower and upper ends of the range are in different units and the exact unit of the

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upper end of the range is unclear. Appropriate correction is required so that the lower and upper ends of the range are both definite and in the same unit of measurement.

At Claim 13, line 1, and Claim 20, line 1, “seed endosperm-preferred promoter” should be changed to --seed endosperm-specific promoter” for clarity.

At Claim 13, line 2, and Claim 20, line 4, the term “elevated” is indefinite because it is not known what it is compared to. Appropriate clarification is required.

At Claim 18, the phrase “seed product” is indefinite. It is not known what is intended by the phrase and/or what is encompassed by the claim. Appropriate correction is required to clarify the claimed invention.

At Claim 18, the term “obtainable” is indefinite because it is not clear whether or not it is obtained. The term should be changed to --obtained--.

At Claim 20, there is a lack of agreement between “seed” (singular) at line 1, and “seeds” (plural) at line 6. Appropriate correction is required.

At Claim 20, there is a lack of agreement between “cell” (singular) at line 2, and “cells” (plural) at line 5. Appropriate correction is required.

At Claim 20, line 5, the second method step “recovering the transformed cells” is incongruous with the first method step of “transforming a host plant cell,” *i.e.* it is unclear what the transformed cell is recovered from. It is recommended that the second method step be deleted.

At Claim 20, line 6, it is unclear to what “therefrom” refers.

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***Claim Rejections - 35 USC § 102***

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claims 1-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Falco *et al.* (U.S. Patent 5,773,691).

The claimed invention is indefinite for the reasons discussed *supra*. In particular, “derivatives” at Claim 8 is indefinite and reads on essentially any protein.

Falco discloses transformed plants, especially corn, comprising seed with enhanced lysine content, obtained by expression of chimeric genes encoding lysine insensitive enzymes or lysine-rich proteins (Abstract; Col. 1, lines 18-30; Col. 6, line 22 - Col. 7, line 44; Col. 9, line 38 - Col. 10, line 37; Col. 30, line 15 - Col. 31, line 62; Examples 22, 23, 25). In particular, <sup>Falco</sup> ~~Applicant~~ teaches said transformed plants wherein the increases in lysine are 10-400% (Col. 6, lines 65-66). <sup>Falco</sup> and ~~Applicant~~ teaches use of an endosperm-specific promoter, including the zein promoter (Col. 19, lines 40-55). Hence, all of the claim limitations have been previously disclosed by Falco.

8. Claims 1, 2, 4-13, 18 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Rao (U.S. Patent 5,885,802).

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The claimed invention is indefinite for the reasons discussed *supra*. In particular, the claim language “or ... and optionally” is indefinite, and hence the claims read on a transformed cereal plant seed with an elevated level of methionine. Also, the claimed increases in amino acid content in Claims 10-12 are not clear.

Rao teaches transformed plants with elevated levels of methionine, a sulfur-containing amino acid, by expression of a mutant barley hordothionin gene with methionine amino acid substitutions (Abstract; Col. 2, lines 19-29; Col. 2, line 66 - Col. 3, line 8). Specifically, Rao teaches transformed cereal crops (Col. 3, lines 55-58). Although Rao does not specifically recite the amount of increase in methionine in transformed plants, the plants of Rao are believed to encompass the claimed invention, particularly given the indefiniteness of the claim language in Claims 10-12. Therefore, all of the claim limitations were previously disclosed by Rao.

#### ***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rao *et al.* in view of Schernthaner *et al.* (EMBO 7: 1249-1255, 1988).

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The claims are indefinite for the reasons discussed *supra*. However, it appears that Applicant broadly claims a transformed cereal plant seed with an elevated level of at least one amino acid, and particularly wherein said amino acid is lysine. Applicant also claims vectors comprising an endosperm-specific promoter operably linked to a gene which encodes a protein with an elevated level of an amino acid, a plant cell transformed therewith, and a method of enhancing the nutritional value of plant seed therewith.

The teachings of Rao are discussed above.

Rao does not specifically teach transformed plants with an elevated level of lysine, and Rao does not teach use of an endosperm-specific promoter.

Schernthaner teaches the zein promoter, and teaches that the promoter has endosperm-specific activity (Abstract; Fig. 4).

It would have been *prima facie* obvious to modify the invention of Rao to substitute lysine rather than methionine in to the encoded hordothionin protein, because they are both nonpolar hydrophobic amino acids and because Rao teaches that threonine, lysine and methionine are all essential amino acids required for animal nutrition which are missing from and need to be increased in crop plants (Col. 1, lines 40-42; Col. 2, lines 8-10). It also would have been obvious to modify the invention of Rao to substitute an endosperm-specific promoter as taught by Schernthaner for the constitutive promoter, because the invention was clearly directed to modification of seed tissue, and especially endosperm. The different promoters are functional

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equivalents, and it would have been obvious to substitute one functional equivalent for another.

One would have had a reasonable expectation of success in view of the success of Rao.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy J. Nelson whose telephone number is (703) 306-3218. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909. The fax phone number for this Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application, or if the examiner cannot be reached as indicated above, should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Amy J. Nelson, Ph.D.

May 17, 1999